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*  
* * * * *                                                         *  
FILE 'USPAT' ENTERED AT 10:48:33 ON 08 APR 1999  
  
* * * * *                                                         *  
*              W E L C O M E     T O     T H E               *  
*             U . S .    P A T E N T     T E X T     F I L E   *  
* * * * *                                                         *
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=> s triglyceride?(p) (fibrate or fenofibrate)

=> d 1-12

George Barnwell, 514/2 [IMAGE AVAILABLE]

6. 5,545,628, Aug. 13, 1996, Pharmaceutical composition containing fenofibrate; Arthur Deboeck, et al., 514/49; 424/1.73, 456, 463, 478, 490, 492; D24/100 [IMAGE AVAILABLE]

7. 5,246,951, Sep. 21, 1993, New benzoselenazolinone compounds; Vincent Galet, et al., 514/359, 598, 640; 548/121; 562/899 [IMAGE AVAILABLE]

8. 5,128,331, Jul. 7, 1992, Method for lowering plasma lipid levels or blood pressure; Lan Nguyen, et al., 514/101, 107, 824 [IMAGE AVAILABLE]

9. 5,043,330, Aug. 27, 1991, Phenol substituted gem-diphosphate derivatives, process for their preparation and pharmaceutical compositions containing them; Lan Nguyen, et al., 514/107; 558/77, 83, 161; 562/19, 21 [IMAGE AVAILABLE]

10. 4,175,130, Nov. 20, 1979, Oxazole- and thiazole-alkanoic acid compounds; Tsutomu Yamanaka, et al., 514/369, 376; 546/269.7, 271.4; 548/187, 228 [IMAGE AVAILABLE]

11. 4,053,635, Oct. 11, 1977, Substituted amides of 3-methyl-4-phenyl-3-butenic acid, with a high hypolipemizing activity; Sergio Gorini, et al., 514/570; 544/176; 564/182 [IMAGE AVAILABLE]

12. 4,008,324, Feb. 15, 1977, Phenoxyalkylcarboxylic acid salt of 1-cinnamyl-4-diphenylmethyl piperazine, method of preparation and antihypercholesteremic; Gunter Metz, et al., 514/255; 544/396 [IMAGE AVAILABLE]

=> d 1-12 kwic

US PAT NO: 5,880,148 [IMAGE AVAILABLE]

L1: 1 of 12

DETDESC:

DETD(40)

In a first series, the plasma levels of total cholesterol, phospholipids and **triglycerides** were evaluated. The results obtained, which are collated in Table I below, show that **fenofibrate** administered on its own causes a significant decrease in the total plasma cholesterol (variation from -31 to -40%), very slightly reduces the plasma phospholipid levels and does not modify the plasma **triglyceride**

levels. When combined with dl-.alpha.-tocopherol acetate, **fenofibrate** generates the same changes, whereas dl-.alpha.-tocopherol acetate administered on its own is inactive.

DETDESC:

DETD(41)

The results in Table I, which are the mean (n=6) .+-.the root-mean-square error, are therefore consistent with the previously disclosed effects of **fenofibrate** and dl-.alpha.-tocopherol acetate on the plasma levels of total cholesterol, phospholipids and **triglycerides**.

DETDESC:

DETD(47)

			0.65 .+-. 0.10
B) Co-micronized feno-			
	3	0.49 .+-. 0.02.star-solid.	
			0.97 .+-. 0.02.star-solid.
			0.44 .+-. 0.03
fibrate (37 mg/kg/d)			
C) dl-.alpha.-Tocopherol			
	3	0.74 .+-. 0.03.star-solid.	
			1.28 .+-. 0.04
			0.72 .+-. 0.10
acetate (55 mg/kg/d).			0.83 .+-. 0.09
B) Co-micronized feno-			
	8	0.46 .+-. 0.02.star-solid.	
			1.09 .+-. 0.02.star-solid.
			0.43 .+-. 0.05
fibrate (37 mg/kg/d)			
C) dl-.alpha.-Tocopherol			
	8	0.69 .+-. 0.02	
			1.18 .+-. 0.05
			0.69 .+-. 0.10
acetate (55 mg/kg/d).			0.82 .+-. 0.12
B) Co-micronized feno-			
	15	0.4i .+-. 0.02.star-solid.	
			1.23 .+-. 0.02
			0.69 .+-. 0.05
fibrate (37 mg/kg/d)			
C) dl-.alpha.-Tocopherol			
	15	0.65 .+-. 0.04	
			1.30 .+-. 0.06
			0.86 .+-. 0.08
acetate (55 mg/kg/d).			1.16 .+-. 0.05
B) Co-micronized feno-			
	27	0.43 .+-. 0.02.star-solid.	

		1.29	+-	0.04
		1.24	+-	0.23
fibrate (37 mg/kg/d)				
C) dl-.alpha.-Tocopherol				
	27	0.65	+-	0.03
		1.35	+-	0.05
		0.94	+-	0.11
acetate	(55 mg/kg/d)	1.30	+-	0.07
		0.99	+-	0.11

Notes:

- (1) Total cholesterol (g/l)
- (2) Phospholipids (g/l)
- (3) **Triglycerides** (g/l)
- (.star-solid.) statistically significant
- (p .ltoreq. 0.05)

US PAT NO: 5,859,051 [IMAGE AVAILABLE]

L1: 2 of 12

SUMMARY:

BSUM(9)

It . . . acids. PPAR.alpha. is also involved with the activity of fibrates in rodents and humans. Fibric acid derivatives such as clofibrate, **fenofibrate**, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma **triglycerides** along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

US PAT NO: 5,847,008 [IMAGE AVAILABLE]

L1: 3 of 12

SUMMARY:

BSUM(9)

It . . . acids. PPARA.alpha. is also involved with the activity of fibrates in rodents and humans. Fibric acid derivatives such as clofibrate, **fenofibrate**, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma **triglycerides** along with moderate reduction in LDL cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

US PAT NO: 5,827,536 [IMAGE AVAILABLE]

L1: 4 of 12

SUMMARY:

BSUM(2)

Fenofibrate is a substance which has been used for more than 20 years in most countries of the world for the treatment of endogenous hyperlipidaemias, hypercholesterolaemias and hypertriglyceridaemias in adults. Prolonged treatment with **fenofibrate** at the rate of 300 to 400 mg per day makes it possible to obtain a reduction in total cholesterol of 20 to 25% and a reduction in the levels of **triglycerides** of 40 to 50%. It thus opposes the development of atherosclerosis.

SUMMARY:

BSUM(24)

The usual fatty solvents, such as the mono-, di- and **triglycerides** of C.sub.8 to C.sub.16 fatty acids derived from vegetable oils, have not made it possible to obtain the required **fenofibrate** solubilities. The addition of surfactants, such as polyglycosylated glycerides, substantially improves the solubilities, however.

US PAT NO: 5,767,066 [IMAGE AVAILABLE] L1: 5 of 12

SUMMARY:

BSUM(18)

Isobutyric acid derivatives include bezafibrate, clofibrate, **fenofibrate** and gemfibrozil. These drugs effectively reduce plasma **triglycerides** and VLDL, raise HDL, and can reduce LDL-cholesterol by up to 18%. Isobutyric acid derivatives cause about a 10% incidence. . .

US PAT NO: 5,545,628 [IMAGE AVAILABLE] L1: 6 of 12

SUMMARY:

BSUM(5)

Fenofibrate or P-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum **triglyceride** levels and/or cholesterol levels. The usual daily dosage is 300 mg which is administered in two or three doses. **Fenofibrate** is absorbed as fenofibric acid which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of **fenofibrate** is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the. . .

US PAT NO: 5,246,951 [IMAGE AVAILABLE] L1: 7 of 12

SUMMARY:

BSUM(522)

The . . . on the day on which the treatment is started. One group receives a placebo. The other group of mice receives **fenofibrate** at a dose of 300 mg.kg.sup.-1 /day. The other groups of mice receive the products of the invention at a dose of 30 mg.kg.sup.-1 /day. An assay of **triglycerides** and total, free and esterified cholesterol reveals a significant decrease in these parameters, greater than that obtained with **fenofibrate** (at a 10-fold higher dose).

US PAT NO: 5,128,331 [IMAGE AVAILABLE]

L1: 8 of 12

DETDESC:

DETD(156)

With . . . close to man (generally greater than 150 mg/dl). For example, in mice receiving a normal diet the plasma cholesterol and **triglyceride** levels are in the range of 100 mg/dl, whereas for rat the comparative values are close to 50 mg/dl. Other. . . a relevant model for testing new agents in comparison to drugs known to be efficacious in human hyperlipidemia (Effects of **Fenofibrate**, Gemfibrozil and Nicotinic Acid and Plasma Lipoprotein Levels in Normal and Hyperlipidemic Mice, a Proposed Model for Drug Screening. Olivier,.

DETDESC:

DETD(176)

TABLE 3

HYPOLIPIDEMIC ACTIVITY OF DIPHOSPHONATES
OF FORMULA (I) AND REFERENCE DRUGS

Compounds (I)	Cholesterol	Triglycerides
	(% control)	(% control)
1	-2	-28
2	+6	-17
4	-12.	.
43	-5	-14
46	+1	-12
47	-31	-45

48	-21	-36
Reference Drugs		
Clofibrate	+4	-5
Gemfibrozil	-7	-35
Fenofibrate	-15	-2

US PAT NO: 5,043,330 [IMAGE AVAILABLE]

L1: 9 of 12

DETDESC:

DETD(394)

With . . . close to man (generally greater than 150 mg/dl). For example, in mice receiving a normal diet the plasma cholesterol and **triglyceride** levels are in the range of 100 mg/dl, whereas for rat the comparative values are close to 50 mg/dl. Other. . . a relevant model for testing new agents in comparison to drugs known to be efficacious in human hyperlipidemia (Effects of **Fenofibrate**, Gemfibrozil and Nicotinic Acid on Plasma Lipoprotein Levels in Normal and Hyperlipidemic Mice, a Proposed Model for Drug Screening. Olivier,. . .

DETDESC:

DETD(415)

TABLE 3

HYPOLIPIDEMIC ACTIVITY OF DIPHOSPHONATES OF FORMULA (I) AND REFERENCE DRUGS		
Compounds	Cholesterol	Triglycerides
(I)	(% control)	(% control)
1	-2	-28
2	+6	-17
4	-12	-1
. . .		
43	-5	-14
46	+1	-12
47	-31	-45
48	-21	-36
Reference Drugs		
Clofibrate	+4	-5
Gemfibrozil	-7	-35
Fenofibrate	-15	-2

US PAT NO: 4,175,130 [IMAGE AVAILABLE]

L1: 10 of 12

SUMMARY:

Table 1

Com- pound	Dose (mg/kg/day)	Decrease (%)			Increase (%)	
		Cholesterol		Triglyceride	Liver Weight	
A	100	40*	33*	5		
B	100	37*	33*	-6		
C	100	40*	29*	15		
D	100	32*	33*	5		
Clo- fibrate	100	32*	34*	17*		

(*:p<0.05)

US PAT NO: 4,053,635 [IMAGE AVAILABLE]

L1: 11 of 12

SUMMARY:

BSUM(9)

TABLE III

hyperlipemia from diet*

	Cholesterolemia	Hepatic	Hepatic
	Triglyceridemia.degree.	Cholesterol.degree.	triglycerides
Treatment	mg/100 ml .+-. SE	mg/100 ml .+-. ES	mg/g fresh tissue
(6)	142.4.+-.7.7(not signif)	91.5.+-.13.6(not si	20.2.+-.0.9(not signific.)
(p<0.02)			37.7.+-.5.6
		gnificat.)	
idem + chlo-			
fibrate			
(9)	138.8.+-.10.7 (" ")	60.0.+-.4.3 (p<0.01)	18.5.+-.1 (" ")
30.3.+-.2.5(p<0.001)			
idem + IIIb			
(7).			

SUMMARY:

BSUM(12)

TABLE IV

hypertriglyceridemia from ethanol*

Triglyceridemia		Significance against
Significance against		sets treated with
Treatment	mg/100 ml .+- . SE	ethanol
	controls	

Controls

(10) 74.20.+- .3.70. . .

idem + I
(9) 275.11.+- .31.63
-- p<0.001

idem + chlo-
(10) 121.50.+- .12.26
-- not significant

fibrate
idem + IIId
(9) 90.0.+- .14.83
-- p<0.05

*Animal: Sprague-Dawley male rat of the average weight of 150.

US PAT NO: 4,008,324 [IMAGE AVAILABLE]

L1: 12 of 12

SUMMARY:

BSUM(31)

Table 1

Normal diet		Hypercholesterol diet	
Reduc-	Reduc-	Reduc-	Reduc-
Cholesterol			
tion			
Triglycerides			
tion			
		Cholesterol	
		tion	

Compound	Triglycerides							
	mg/kg	mg %		mg %		mg %		tion
	mg/%	%	mg %	%	mg %	%	mg %	%
<hr/>								
Control	--.	.	65.8*	-24.4				
					288.6	-9.5		
							70.9*	--17.6
Control	--	76.9	--	123.8	--	358.6	--	86.4
Clo-								
fibrate								
250		56.1*						
			27.0					
				66.5*				
					46.3			
					347.9	3.0		
							75.6	12.5
Control	--	95.7	--.	.				

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